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## Editorial

# Thrombotic obstruction in left-side prosthetic valves: Role of thrombolytic therapy<sup>☆</sup>



### Keywords:

Prosthetic valve thrombosis

Thrombolytic treatment

Mechanical valve thrombosis

Streptokinase

## 1. Introduction

Prosthetic valve thrombosis (PVT) is a complication that endangers the life of patients with prosthetic heart valves. The incidence of PVT can be as high as 13% during the first year in any valve position and even 20% for mechanical prostheses in the tricuspid position. At any time, for prostheses in the mitral and/or aortic position, the overall incidence is 0.5–6% per patient-year, the highest in the mitral position. The risk of a thrombus, in spite of adequate oral anticoagulation, has been estimated at between 1% and 4% per year. The prevalence of asymptomatic nonobstructive PVT is 50%. During the early postoperative period, nonobstructive PVT may reach 10%.<sup>1</sup>

It is mandatory that the antithrombotic prophylaxis in these patients achieves an INR range of 2–4 as recommended by guidelines regardless of thrombogenic risk factors.<sup>2</sup>

PVT is classified as obstructive if there is a limitation of the leaflet mobility and a thrombus is present, clinically characterized by progressive heart failure, pulmonary edema or cardiogenic shock, and/or systemic embolism. In relation with auscultation, occluder clicks are typically muffled or absent. Also, stenotic or regurgitant murmurs may be heard.

PVT is not obstructive when there is a thrombus but normal mobility of the leaflet, and this may not only cause stroke or peripheral embolism, but may also remain asymptomatic in about 50% of cases.

Patient-related risk factors for PVT are: inadequate anticoagulation, left ventricular dysfunction, atrial fibrillation, pregnancy (hypercoagulability status), infection, early postoperative period, and spontaneous echocontrast as diagnosed by transoesophageal echocardiography (TEE).

## 2. Diagnosis

A high degree of clinical suspicion will lead to the diagnosis of PVT. The clinical history and cardiac auscultation are often suggestive. Compliance with an adequate anticoagulant therapy should be verified, including the INR values in preceding weeks, since sub-therapeutic levels are important diagnostic clues. The patient and/or relatives may report disappearance or attenuation of the prosthetic noise, which should be confirmed by auscultation. The latter may reveal a previously nonexistent murmur.

Imaging techniques are basic tools in diagnosing PVT. Fluoroscopy and cardiac computed tomography can help to detect alterations in the movement of the prosthetic leaflets, such as variations in the opening and closure angles.

Transthoracic echocardiography (TTE) is indicated to patients with suspected PVT in order to assess hemodynamic severity and follow resolution of valve dysfunction.

TEE is the best diagnostic tool to evaluate the mobility of the valve and the thrombus size. It may also be useful to differentiate thrombus from pannus as the mechanism of prosthetic obstruction. Thrombus is larger, more mobile, and lower in density than pannus. Thrombus size is an important independent predictor of lack of success of thrombolysis in the PVT.

Real-time 3-dimensional (3D) TEE provides a live “en face” surgical view of the mitral valve, which can improve diagnostic accuracy for detecting mitral prosthetic valve pathologies. Real-time 3D TEE can detect prosthetic mitral thrombosis that could be missed on a 2D TEE and cause thromboembolic events.<sup>3</sup>

<sup>☆</sup> This editorial is pertaining to the article: Successful use of Tenecteplase in a patient with recurrence of prosthetic mitral valve thrombosis.

### 3. Treatment

PVT can be treated with three therapeutic modalities: surgery, thrombolysis, and anticoagulation. Surgery has been traditionally the first choice therapeutic for PVT (prosthetic valve replacement or thrombectomy).

The evidence supporting the guidelines on PVT is scarce and recommendations from various organizations are not uniform.<sup>4</sup> The European Society of Cardiology proposes surgery as the initial treatment, regardless of clinical status and the size of the thrombus. The Society of Heart Valve Disease recommends that the first choice should be thrombolysis in all cases of PVT, unless such treatment is contraindicated. The American Heart Association and American College of Cardiology reserves thrombolysis only for patients with PVT of recent onset (<14 days) of New York Heart Association (NYHA) functional class I to II symptoms, and for a small thrombus (<0.8 cm<sup>2</sup>). The American College of Chest Physicians recommends that the main criterion in the therapeutic decision should be the size of a thrombus. The American College of Chest Physicians indicates thrombolysis as the treatment choice if the thrombus has an area of 0.8 cm<sup>2</sup> and surgery in cases of older thrombi.

Despite advances in surgical techniques, anesthetics, and perioperative care, surgical mortality rates are main high, especially in patients with PVT and NYHA functional class III–IV.

Durrleman and coworkers presented a series of 39 patients with PVT over a 20-year period who underwent thrombectomy or valve replacement, with an associated mortality of 25% and 41%, respectively. Oskokeli et al. in 30 patients with left-side PVT, reported a postoperative early hospital mortality of 7.1% (NYHA classes II–III) and 31.3% (NYHA IV) and Toker et al. reported in 63 cases a total mortality of 20.6%. Keuleers reported a mortality rate of 11% in 18 patients with PTV treated with emergency surgery. Ermis obtained 16.6% surgical mortality in 18 patients with PVT.

The effective implementation of thrombolysis in PVT in 1971, by Luluaga<sup>5</sup> started the debate in determining the first therapeutic option for these patients, i.e. surgery or thrombolysis, for which the debate has not ended.

In this issue of *Indian Heart Journal*, Lahoti and Goyal publish a manuscript entitled “Thrombolytic therapy for left side prosthetic valve thrombosis: Short and long term follow up study.”<sup>6</sup> In this article, they report a series of 11 patients with a diagnosis of PVT who received thrombolytic therapy with streptokinase. They were evaluated at 24 h, 72 h, and the 7th

day after the intervention. Long-term follow-up was extended by seeing the patients every 3–6 months. The treatment was successful in 8 patients (73%), whereas three patients died, who had presented with functional class NYHA IV with hypotension and cardiogenic shock. It seems unlikely that the alternative, surgical treatment would have proven successful in these seriously ill patients. The authors report no complications of the thrombolytic therapy reported. During extended follow-up, survival was between 1 and 10 years with an average of 5 years up to the present.

In India, PVT occurrence is high, with 6.1% in the first 6 months after replacement of the valve. While thrombolysis has been gaining ground universally, the limited availability and high cost of surgery have turned fibrinolytic therapy into the first line therapy for PVT in most developing countries. Between 1990 and 2015, several series of cases with diagnostics PVT treated with thrombolysis have been published, with a total number of patients reported on is of 413 with an acceptable initial success rate of 81.1% (Table 1). The risk of systemic embolism, bleeding, and recurrence are crucial parameters that form part of the recommendations of the latest guidelines. Favorably, thrombolysis has a high rate of success in patients with hemodynamic instability. If partial clot lysis can be achieved by thrombolysis, this may still be useful, for patients can then undergo surgery with improved hemodynamic conditions and thus at lower risk. Other arguments that favor thrombolysis are its widespread availability, easy application, and low cost in comparison with surgery.<sup>7</sup>

### 4. Recent evidence

In an attempt to clarify the best therapy treating PVT, several meta-analyses and systematic reviews have been published in recent years.

Karthikeyan and colleagues<sup>8</sup> compared emergency surgery with fibrinolysis in left-sided prosthetic heart valve thrombosis. This overview included seven studies with 690 episodes of PVT, 446 treated with surgery, and 244 with thrombolysis. The primary outcome variable was the restoration of valve functions. The authors found no clear differences in the main outcome between patients treated surgically (446) of whom 60 died (13.5%) and 244 patients treated with thrombolysis, of whom 22 died (9%). Despite these results suggesting the contrary, the study concluded that in experienced centers, urgent surgery should probably be preferred over thrombolysis

**Table 1 – Indian series of patients with PVT and thrombolytic therapy (years 1990–2015).**

Study (First Author, Journal, Year of publication)	Enrolment period	Thrombolysis samples size	Efficacy rate (n%)
Vasan ( <i>Am Heart J</i> 1992)	1990–1991	16	16/100
Reddy ( <i>Ann Thorac Surg</i> 1994)	1990–1993	44	39/88.6
Rajasekhar ( <i>Indian Heart J</i> 1994)	1992–1993	13	12/92
Agrawal ( <i>Indian Heart J</i> 1997)	1987–1997	42	37/88
Gupta ( <i>Am Heart J</i> 2000)	1990–1999	110	101/91.8
Kumar ( <i>Indian Heart J</i> 2001)	1994–2000	48	42/87.5
Karthikeyan ( <i>Circulation</i> 2009)	2004–2007	119	70/59
Sharma ( <i>J Assoc Phys India</i> 2012)	–	10	10/100
Lahoti and Goyal ( <i>Indian Heart J</i> 2015)	–	11	8/72.7
Total	1990–2015	413	335/81.1

for treating left-sided PVT. This conclusion was mainly based on a lower rate of thromboembolic events, major bleeding, and recurrent PVT.

Huang and co-workers<sup>9</sup> conducted a literature survey, including 17 studies comprising 756 patients who had received thrombolytic therapy and 13 studies comprising 662 patients who had received surgery. The survey's results revealed 30-day mortality in the group treated with surgery at 15% (98 deaths in 662 patients) vs. 8% (61 deaths in 756 patients) in the thrombolysis pooled. The rates of recurrence and complications, however, were higher in patients treated with thrombolysis. On this basis, they recommended thrombolysis as a first choice for patients in NYHA Class I/II with severe comorbid conditions associated with a high surgical operative mortality and if surgery is not available, the patient refuses surgery or “small thrombus” – area < 0.8 cm<sup>2</sup>. Initially, surgery may be the preferred therapy for patients in NYHA functional Class III/IV and with a large thrombus (area ≥ 0.8 cm<sup>2</sup>).

In 2014, we published a meta-analysis and a systematic review that included 48 studies with 10 or more patients.<sup>10</sup> The total number of patients was 2239. Twenty-seven studies or study arms were evaluated with 1132 patients in the surgery cohort and 26 studies with 1107 patients were included in the thrombolysis cohort. There was a highly significant difference in mortality between the two groups: surgery, 18.1% (CI, 14.6–22.1%) and thrombolysis, 6.6% (CI, 4.8–9.9%) ( $P < 0.001$ ). A trend of mortality increment directly associated with the proportion of patients in NYHA class IV appeared in patients with surgical treatment. Subgroup analysis revealed that mitral valve thrombosis showed similar mortality to the general analysis: 6.5% (4.2–9.9%) related to thrombolytic therapy ( $n = 307$  in 14 studies) and 20.5% (14.9–27.7%) related to surgery ( $n = 196$  in 11 studies) ( $P < 0.001$ ). Another subgroup analysis for left-side valve thrombosis also had similar results: 6.5% (4.3–9.7%) related to thrombolytic therapy ( $n = 345$  in 14 studies) and 17.8% (14.1–22.4%) related to surgery ( $n = 364$  in 12 studies) ( $P < 0.001$ ). The incidence of a stroke was similar in both treatment groups: surgery, 5.6% and thrombolysis, 4.3% ( $P = 0.29$ ). As expected, embolic events were more common in the thrombolysis group (4.6% vs. 12.8%,  $P < 0.01$ ). However, there was no statistical difference in the bleeding rate (4.6% and 6.8%) or intracranial hemorrhage (2.1% vs. 3.3%,  $P = 0.24$ ).

Finding an answer to the therapeutic dilemma in randomized trials is unlikely due to the sample size that is required. Based on our results, it would be necessary to recruit at least 1024 patients in each arm (2048 patients total) to evaluate the combined endpoints of stroke and death in a randomized trial with 80% power and 5% alpha error.

Even considering the possibility of a multicenter study, it would be difficult, if not impossible to achieve such sample size. Another possible solution could be a large prospective observational multicenter registry.

The outcome of this meta-analysis suggests a leading role for thrombolytic treatment in patients with PVT.

Based on recent evidences and our personal experience, new guidelines should incorporate thrombolysis as a first choice treatment in patients with left-side PVT with NYHA functional class III–IV, because of the effectiveness, safety profile, availability, simplicity, and low cost of thrombolysis.

Surgery should be reserved for patients with specific contraindications for thrombolysis in PVT (large left atrial thrombus >5 mm ischemic stroke in the first 4–6 weeks and first 4 days of perioperative period) or if thrombolysis fails.

## Conflicts of interest

The authors have none to declare.

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